

REMARKS

Claim 1 has been amended to recite, “A compound 12 to 30 nucleobases in length comprising at least 12 linked nucleosides of a nucleotide sequence selected from the group consisting of SEQ ID NOs: 26-84.” Support for this amendment may be found at least at pages 12, 82, and 83 of the specification as originally filed. Claims 15 and 16 have been added. Support for new claims 15 and 17 may be found at least at pages 82 and 83 of the specification as originally filed. Claims 1-9 and 11-16 are pending.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-9 and 11-14 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written descriptive support in the application. The Examiner argues that the specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus claimed. *Office Action* at 2. The Office Action mailed March 5, 2007 states, “The specification discloses antisense oligonucleotides 20 nucleotides in length and fully complementary to SEQ ID NO: 17. The specification does not disclose any other sequences, including any sequences with less than 100% identity to the complement of SEQ ID NO: 17....” *Office Action* at 2-3. Thus, the Examiner concludes that the specification and claims do not adequately teach a representative number of species for the broad genus claimed. Applicants respectfully traverse this rejection.

Applicants disagree with the assertion that, “The specification does not disclose any other sequences, including any sequences with less than 100% identity to the complement of SEQ ID NO: 17.....” *Office Action* at 3. Sequences having less than 100% identity are described at least on page 9 of the specification as originally filed. For example, the specification at page 9 states, “It is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable.” Later, the specification states at page 9, “Antisense and other compounds of the invention which hybridize to the target and inhibit expression of the target are identified through experimentation, and the sequence of these compounds are hereinbelow identified as preferred embodiments of the

invention.”

Similarly, oligonucleotides having lengths of 8 to 50 nucleobases are described at least on page 12 of the specification as filed. For example, the specification at page 12 states, “The antisense compounds in accordance with this invention preferably comprise from about 8 to about 50 nucleobases....Particularly preferred antisense compounds are antisense oligonucleotides, even more preferably those comprising from about 12 to about 30 nucleobases.”

Thus, Applicants have provided written description directed both to the degree of complementarity as well as the length of antisense compound. Although there is no requirement that the specification provide examples detailing all workable degrees of complementarity and workable lengths, Applicants have provided a number of explicit examples of antisense oligonucleotides falling within the genus claimed, such that one of ordinary skill in the art would recognize Applicants to be in possession of the claimed invention. It is sufficient that Applicants have provided description stating that varying degrees of complementarity are workable and that varying lengths of antisense oligonucleotides are workable.

Accordingly, Applicants respectfully request withdrawal of the written description rejection under 35 U.S.C. §112, first paragraph.

REJECTION UNDER 35 U.S.C. §103

Claims 1-9 and 11-14 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Korsmeyer (USPN 6,500,626), Dibbert et al. (1999, Proc. Natl. Acad. Sci. 96:13330-13335) and Manfredini et al. (1998, Antisense Nucleic Acid Drug Dev. 8:341-350), the combination in view of Milner et al. (1997, Nature Biotech. 15:537-541) and McKay et al. (USPN 6,133,246). The Examiner alleges that Korsmeyer, Dibbert et al., and Manfredini et al. teach the inhibition of expression of BCL-2 associated x (BAX) protein, using antisense oligonucleotides. *Office Action* at 5. The Examiner alleges that Milner et al. teaches methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro, including the 5', 3', and stop codon regions of the target gene. *Office Action* at 6. The Examiner alleges that McKay et al. teaches

the administration to cells in vitro of colloidal dispersion compositions comprising antisense oligonucleotides between 8 and 50 nucleobases in length which optionally comprise modified internucleotide linkages including phosphorothioate linkages, modified nucleobases including 5-methylcytosine, modified sugar moieties including 2'-O-methoxyethyl sugars, and wherein the antisense is optionally a chimeric oligonucleotide, and which antisense targets the various regions of recombinant nucleic acid, including the 3' UTR region of a target gene. *Office Action* at 6. The Examiner also alleges that McKay et al. teaches the in vitro inhibition and screening of modulators. *Office Action* at 6. The Examiner asserts that it would have been obvious to design and use antisense oligonucleotides to inhibit BAX using screening assays taught in Milner et al. and McKay et al. *Office Action* at 7. Applicants respectfully traverse.

As amended, claim 1 recites "A compound 12 to 30 nucleobases in length comprising at least 12 linked nucleosides of a nucleotide sequence selected from the group consisting of SEQ ID NOs: 26-84," which is not disclosed by any of Korsmeyer, Dibbert et al., Manfredini et al., Milner et al., and McKay et al. Because none of the cited references, alone or in combination, teach each and every element of the claimed invention, Applicants respectfully request that the Examiner withdraw the rejection of claims 1-9 and 11-14 as obvious over Korsmeyer, Dibbert et al., and Manfredini et al. in view of Milner et al. and McKay et al.

APPLICANTS: Zhang et al.
SERIAL NO: 10/728,509

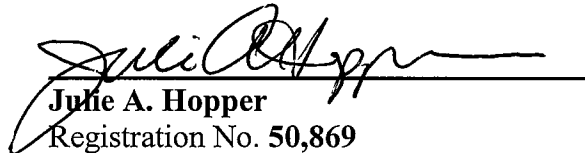
DOCKET NO: ISPH-0803 (ISIS.068C1)

CONCLUSION

In view of the above amendments and remarks, Applicants respectfully request withdrawal of the pending rejections and reconsideration of the claims is respectfully requested. Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. If the Examiner believes that there are any remaining issues in the case that could be resolved by a telephonic interview, the Examiner is encouraged to contact the Agent listed below to discuss any outstanding matters.

Please charge any additional fees, including any fees for additional extension of time, or credit any overpayment to Deposit Account No. 50-0252.

Respectfully submitted,


Julie A. Hopper
Registration No. 50,869

Date: **August 6, 2007**

ISIS Pharmaceuticals, Inc.
1896 Rutherford Rd.
Carlsbad, CA 92008
Telephone: (760) 603-2794
Facsimile: (760) 603-3820